Association between Helicobacter pylori and Iron Deficiency Anemia in Preschool Children

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ABSTRACT

Background: Helicobacter pylori is a gram-negative helical microaerophilic flagellated bacterium contained by a majority of the world's population in the sterile gastric mucosa. It is considered as a significant pediatric gastroenterology pathogen that is acquired in early infancy.

Objective: This study aimed to detect Helicobacter pylori infection in preschool children with iron deficiency anemia and compare them to a control healthy group.

Patients and Methods: The present study was a single blinded randomized controlled interventional trail that was conducted in Pediatric and Clinical Pathology Departments, Zagazig University Children Hospital during the period from August 2017 to May 2018. 44 patients that were randomly divided into 2 groups. Group 1 included 22 diagnosed as iron deficiency anemia with Hb less than 11g/d. Group 2 included 22 apparently healthy children.

Results: In the present study, we used H. pylori stool Ab test to detect Helicobacter pylori infection in the children of the study and it is found that there was increased incidence of H. pylori infection in group I (77.3% vs 4.5% in group II).

Conclusions: There was significant increased incidence of Helicobacter pylori infection in children with iron deficiency anemia and children with refractory iron deficiency anemia compared to healthy ones. This indicates that Helicobacter pylori may be one of the significant causes of iron deficiency anemia and refractory iron deficiency anemia.

Keywords: Helicobacter pylori, Iron Deficiency Anemia , Preschool children.

INTRODUCTION

Anemia is characterized by a decline in total hemoglobin, or red blood cell count. Iron deficiency anemia is a type of anemia due to lack of enough iron to shape normal red blood cells. Iron deficiency anemia is usually caused by inadequate iron intake, chronic blood loss or a combination of both. Iron deficiency anemia is the world's most common cause of anemia **(1).**

Pediatric Nutrition Surveillance System Report indicated a rise in the incidence of anemia in children with low incomes. Anemia should not be treated as a diagnosis but as a finding that needs further investigation**.** It is usually caused in children by decreased RBCs development or increased RBCs turnover. Most children suffering from moderate anemia have no signs or symptoms. Some may show shortness of breath with pallor, irritability, or palpitations. Physical exams can show tachypnea, tachycardia, and heart failure, especially in children with severe or acute anemia **(2)**.

Iron deficiency anemia is characterized as a hemoglobin below the fifth percentile for age normal caused by iron deficiency. Most studies showed that the cut-off point was about 11g/dL (-2 SD lower than mean) **(3).** Iron deficiency (ID) and iron-deficiency anemia (IDA) remain of concern worldwide. Iron is the most common single nutrient deficiency among children in the developing world. Across industrialized nations, IDA remains is a common cause of anemia across young children following a demonstrable decrease in prevalence. However, the suggestion that the more common ID without anemia may also adversely affect long-term neurodevelopment and behavior, which is perhaps more significant than anemia itself, and that some of these effects may be irreversible **(4).**

Helicobacter pylori is a gram-negative microaerophilic flagellated bacterium found in majority of the world's population's gastric mucosa. The presence of bacteria in the stomach was already established as in the late 19th century **(5).** Helicobacter pylori (H. pylori) is a major pediatric gastroenterologic pathogen that is acquired in early childhood, and are more common in developing countries. These bacteria infect more than half of the world's population. Infection rates in both sexes are similar, although some studies reported a slight increase in male predominance. Prevalence increases with age and is more frequent in Asians and Africans. The clinical effects of this infection are still in the evolution stage in children **(5).**

Helicobacter pylori is associated with a number of extra-gastric disorders including iron deficiency anemia, chronic idiopathic purpura, growth retardation and diabetes mellitus **(6).** Several reports indicated a

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correlation between H. pylori Infection and anemia, ID and IDA although the extent of the interactions has not been determined. Studies on the epidemiology have shown that H. seropositivity of the pylori is correlated with low serum ferritin. Infection with helicobacter pylori affects the stomach body and initiates the production of atrophic body gastritis, which may in turn cause decreased gastric acid secretion and increased intragastric pH. H. pylori infection adversely affects the composition of the gastric juice; both of which are essential to normal iron absorption in terms of its acidity and ascorbate content. Such findings suggest that in patients with H. pylori gastritis and IDA, the physiological mechanisms needed to absorb food iron in the duodenal mucosa are impaired [7].

Other potential methods for explaining the relation between H. pylori gastritis and IDA included occult gastrointestinal bleeding and dietary iron resistance from bacteria. Some refractory IDA patients do not have gastrointestinal symptoms, yet H. Pylori gastritis is the primary cause of anaemia [8, 9]. Several studies indicated that patients with reported H pylori infection and IDA found that increments in Hb, serum iron, and serum ferritin from baseline to end-point were significantly higher with anti-H. Pylori, plus oral iron relative to oral iron alone [8]. Therefore, the aim of this study was to correlate between H. pylori infection and iron deficiency and iron stores in children.

PATIENTS AND METHODS

The present study was a single blinded randomized controlled interventional trail that was conducted in Pediatric and Clinical Pathology Departments, Zagazig University Children Hospital in the period from August 2017 to May 2018. 44 patients were randomly divided into 2 groups. Group 1 included 22 diagnosed as iron deficiency anemia with Hb less than 11g/d. They were 11 males (ages ranged from 2-6 years) and 11 females (ages ranged from 2-6) years. Group 2 included 22 apparently healthy children. They were 11 males (ages ranged from 2-6 years) and 11 females (ages ranged from 2-6) years. All children who were diagnosed as IDA, had H. pylori Ab positive or both, have received their treatment and were followed up by laboratory investigations until complete recovery.

Inclusion criteria: Children from both sexes their ages ranged from 2-6 years. Children diagnosed with iron deficiency anemia with Hb less than 11g/d according to WHO description [10].

Exclusion criteria: Children with other types of anemias. Children with chronic illnesses (e.g. CRF, CHF or chronic hemolytic anemias). Children on iron supplementation. Children with other parasitic infestations.

Methodology: All children included in this study were subjected to the following:

History taking: Age, sex, residence and social standard based on kuppuswamy socioeconomic status scale (education score, occupation score and monthly family income) etc.

Family history: Birth order in the family. History of H. pylori infection and iron deficiency anemia, ulcer disease and GI conditions (e.g. Crohn disease etc.…) among family members and consanguinity.

Past history: Parasitic infestation, bleeding from any site, abdominal pain (character, location, frequency, duration, severity, exacerbating and alleviating factors), medications (prescribed and over the counter), previous diagnostic testing and specific therapy in the GI tract, bowel habits and description of stool or halitosis and vomiting with description of gastric material.

Dietary history: Intake of healthy food, appetite condition and weight changes.

Clinical assessment:

A – General examination including:

General appearance: (skin and conjunctiva for pallor).

Anthropometric measurements: Includes measurements of weight in kg, height in cm and body mass index (BMI); height and weight measured and plotted on Egyptian growth charts. Body mass index (BMI) was calculated as:

$$\mathbf{BMI} = \frac{\mathbf{Weight\ (kg)}}{\mathbf{Height\ (m^2)}}$$

B – Systemic examination including:

Abdominal examination: Inspection (for distensions and sites of previous operation), palpation (for tenderness, rigidity, masses etc.), percussion (shifting dullness) and auscultation (intestinal sounds increased in case of pain).

Other systems examination: Respiratory system (tachypnea and dyspnea), cardiovascular system (heart rate, pulses, capillary refill, murmur of hyperdynamic circulation, etc.) and central nervous system (mental status).

Lab Investigations: The following investigations were done for all groups of the study:

Routine Laboratory investigations: Complete blood picture (Hb, HCT, RBCs & WBCs), blood indices (MCV & MCHC), serum iron (ug/ml), serum ferritin (ng/ml) and total iron binding capacity (ug/ml).

Special Laboratory investigations: Assay for H. pylori Ab by strip test.

Sample collection:

Venous blood was obtained from the children (3cm) under aseptic condition, 1ml on EDTA blood

tube for CBC and 2ml were dispensed into dry glass test tubes for clotting and retraction to take place. Sera were obtained after samples were centrifuged at 2000 g for five minutes and stored at -20°C until assayed for laboratory investigations.

Ethical Clearance:

Recorded informed consent for inclusion in the study was received from the patient's parents. **Approval for the research was obtained from the Departments of Pediatrics and Clinical Pathology, Zagazig University Hospitals, following approval of the Institutional Review Board (IRB).** The research was carried out for studies involving humans in compliance with the code of ethics of the World Medical Association (Decleration of Helsinki).

Statistical analysis

Based on Microsoft Excel software, data collected throughout history, basic clinical evaluation, laboratory tests and outcome measures were marked, entered, and analysed. The data were then imported into the Social Sciences Statistical Package (SPSS version 20.0) software for analysis. Qualitative data were represented as number and percentage, quantitative continuous groups were represented by mean ± SD. the following tests were used to test for meaning differences: Difference and combination of qualitative variable by Chi square test (X^2). Differences by t test or Mann Whitney between measurable and independent groups. For significant results, P value was set at ≤ 0.05 & < 0.001 for high significant results.

RESULTS

There was no significant difference between studied groups regarding breast fed distribution or formula fed history (Table 1).

There was no significant difference between groups regarding weight, height or BMI (Table 2).

Table (3) showed that iron supplement significantly associated with cases as 77.3% of cases had iron supplement while only 27.3% of control had it.

Table (4) showed that loss of appetite was significantly associated with cases as 68.2% of cases had loss of appetite while only 18.2% of control had it. In addition, fatigue was distributed as 63.6% & 9.1% between cases and control respectively with significant difference between them. Recurrent abdominal pain and pallor also were significantly associated with cases as they were distributed in cases as 59.1% and 18.2% respectively while in control 4.5% and 0% respectively.

Table (5) showed that cases were significantly lower in all parameters except for RBCs and MCHC. Studied groups showed that case group had significantly lower values of Hb, Hct, MCV and MCH compared to control group.

Table (6) showed that serum iron and s. ferritin were significantly lower in cases.

Table (7) showed that helicobacter pylori was significantly associated and risky for anemia as it was +VE in 77.3% of cases while it was +VE in only 4.5% of control group with significant risk (P=0.00** & OR=71.4).

Table (1): Nutritional history of studied groups

			Group		Total	X2	P
			Control	Case			
Breast Fed	No	N	9	8	17	0.096	0.75
		%	40.9%	36.4%	38.6%		
	Yes	N	13	14	27		
		%	59.1%	63.6%	61.4%		
Formula Fed	No	N	13	14	27	0.096	0.75
		%	59.1%	63.6%	61.4%		
	Yes	N	9	8	17		
		%	40.9%	36.4%	38.6%		
Total		N	22	22	44		
		%	100.0%	100.0%	100.0%		

Table (2): Weight, height and BMI distribution between groups

	Case (N=22)	Control (N=22)	t	P
Wight (kg)	13.31 ± 1.75	13.04 ± 1.61	0.536	0.595
Height (cm)	98.63 ± 8.9	97.22 ± 6.7	0.591	0.558
BMI (kg/m^2)	13.77 ± 1.67	13.85 ± 1.63	-0.142	0.888

Table (3): Iron supplement distribution between groups

			Group		Total	X2	P
			Control	Case			
Iron Supplement	No	N	16	5	21	11.02	0.001**
		%	72.7%	22.7%	47.7%		
	yes	N	6	17	23		
		%	27.3%	77.3%	52.3%		
Total		N	22	22	44		
		%	100.0%	100.0%	100.0%		

Table (4): Symptoms and signs distribution between studied groups

			Group		Total	X^2	P
			Control	Case			
Loss appetite	No	N	18	7	25	11.2	0.001**
		%	81.8%	31.8%	56.8%		
	Yes	N	4	15	19		
		%	18.2%	68.2%	43.2%		
Fatigue	No	N	20	8	28	14.14	0.00**
		%	90.9%	36.4%	63.6%		
	Yes	N	2	14	16		
		%	9.1%	63.6%	36.4%		
Recurrent abdominal pain	No	N	21	9	30	15.08	0.00**
		%	95.5%	40.9%	68.2%		
	Yes	N	1	13	14		
		%	4.5%	59.1%	31.8%		
Abdominal distension	No	N	20	15	35	3.49	0.062
		%	90.9%	68.2%	79.5%		
	Yes	N	2	7	9		
		%	9.1%	31.8%	20.5%		
Pallor	No	N	22	18	40	4.4	0.036*
		%	100.0%	81.8%	90.9%		
	Yes	N	0	4	4		
		%	0.0%	18.2%	9.1%		
Total		N	22	22	44		
		%	100.0%	100.0%	100.0%		

Table (5): CBC distribution between studied groups

	Case (N=22)	Control (N=22)	t	P
HB g/dl	10.04 ± 0.8	13.25 ± 1.61	-8.330	0.00**
HT %	30.77 ± 3.9	39.68 ± 5.18	-6.385	0.00**
RBCs (million/mm^3)	4.06 ± 0.63	4.42±0.6	-1.948	0.058
MCV (Fl)	73.01 ± 11.6	91.59 ± 4.0	-7.093	0.00**
MCH (pg)	23.82 ± 2.29	29.62 ± 1.39	-10.136	0.00**
MCHC (g/dl)	32.24 ± 1.86	32.34 ± 0.69	-0.225	0.823

Table (6): Iron profile distribution between groups

	Case (N=22)	Control (N=22)	t	P
Serum iron (μG/ml)	**49.65 ± 16.96**	**76.52 ± 15.63**	**-5.461**	**0.00****
Total iron binding capacity (TIBC) (μG/dl)	**332.3 ± 59.9**	**336.23 ± 49.4**	**-0.237**	**0.814**
S. ferritin (nG/ml)	**41.22 ± 10.45**	**111.7 ± 25.48**	**-6.143**	**0.00****

Table (7): Helicobacter pylori distribution between studied Groups

			Group		Total	X2	P	OR (CI)
			Control	Case				
Helicobacter pylori	-VE	N	21	5	26	24.06	0.00**	71.4 (6.7-1833.3)
		%	95.5%	22.7%	59.1%			
	+VE	N	1	17	18			
		%	4.5%	77.3%	40.9%			
Total		N	22	22	44			
		%	100.0%	100.0%	100.0%			

DISCUSSION

In this study in group I (iron deficiency anemia) the percent of low socioeconomic standard was 40.9%, moderate socioeconomic standard was 40.9%, high socioeconomic standard was 18.2%. While in group II (controls) the percent of low socioeconomic standard was 27.3%, moderate socioeconomic standard was 54.5%, high socioeconomic standard was 18.2%. There was no significant difference between groups regarding socioeconomic standard however low social class associated with cases but not significantly as it represented 40.9% of cases. **Sachan *et al.*** [(10)] reported that IDA significantly increased among search group members who came from low socioeconomic standard.

In this study, there was no significant statistical difference concerning anthropometric measurements between the two studied groups. On the contrary, **Mahmoud *et al.*** [(11)] confirmed that the anemic condition significantly affected the young children who were found to have a lower mean weight and shorter stature. **Telatar *et al.*** [(12)] studied the impact of anemia during pregnancy on the anthropometric measurements of Saudi newborns. The authors found a significant negative effect of anemia on neonatal anthropometric measurements. **Dakshayani** [(13)] showed significant declines in anthropometric measurements of neonates born to anemic mothers. In addition, they reported the same result. On the other hand, **Ayoya *et al.*** [(14)] considered treated short stature and stunting as predictors of infant anemia.

In our study, regarding complaints of studied groups, we revealed that there was significant increase in incidence of recurrent episodes of mild abdominal pain, fatigue (reduced effort) and loss of appetite in case group members vs most of controls reported no complaints, with significant statistical difference between the two groups. This finding is in accordance with **Jeffery** [(15)] who demonstrated that fatigue was regularly reported in children with iron deficiency anemia.

Regarding the nutritional status, there was no substantial difference between the groups studied whether breast-fed distribution or formula fed history. In accordance with our results, **Henry *et al*** [(16)] showed that many studies in rural Alaska concluded that inadequate iron intake was unlikely to cause iron deficiency anaemia.

As regards the laboratory data of the studied groups, the present study showed that there was significant lower values of CBC parameters in case group as compared to control group. This finding is in accordance with **Mahmoud *et al.*** [(11)] who stated that there were significant lower CBC values, in IDA children compared to the non-anemic controls.

There was a significant decrease in serum iron (mean 49.65±16.96), serum ferritin (mean 41.22±20.45) while the decrease in total iron binding capacity was not significant (mean 332.3±59.9) in case group as compared to control group. These findings are in agreement with those of **Terri *et al.*** [(1)] who stated that iron studies diagnostic for iron deficiency anemia consist of a low serum iron (< 7. 1 mg/l), a low serum ferritin (< 30 ng/ml).

Regarding H. pylori infection among the studied groups, our study revealed that in group I 77.3% of the children were affected with H. pylori while in control group 4.5% of the children were affected with H. pylori. These results coincide with those of **Kiran *et al.*** [(7)] who reported the prevalence of H. pylori infection was 19 per cent of anemic population. Equally, **Henry *et al.*** [(16)] prove that H. pylori infection may be a significant risk factor for iron deficiency and iron deficiency anemia

among children in rural Alaska, and probably in other parts of the world where such conditions are highly common. In contrast to previous study, **Parkinson *et al.*** [(17)] did not find an association between iron deficiency and H. pylori seropositivity. In addition, **Queiroz *et al.*** [(18)] showed very low prevalence of H. pylori in the UK cohort. Infection with H. pylori in an ethnically diverse group of children may account for the lack of association between the infection and iron deficiency / IDA parameters.

CONCLUSION

There was significant increased incidence of Helicobacter pylori infection in children with iron deficiency anemia and children with refractory iron deficiency anemia compared to healthy ones, which indicate that Helicobacter pylori may be one of the significant causes of iron deficiency anemia and refractory iron deficiency anemia. Rural residence with poor hygienic measures with suggestive symptoms as recurrent abdominal pain, reduced effort, loss of appetite and signs as pallor associated with low serum ferritin increase the suspicion of Helicobacter pylori infection as a possible cause of iron deficiency anemia**.**

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